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General Synthesis of Chiral β-Hydroxy Sulfones *via* Enantioselective Ruthenium-Catalyzed Hydrogenation

P. Bertus, P. Phansavath, V. Ratovelomanana-Vidal, J.-P. Genêt
Laboratoire de Synthèse Sélective Organique et Produits Naturels (UMR 7573), Ecole Nationale Supérieure de Chimie de Paris,
11 rue P. et M. Curie, 75231 Paris Cedex 05, France.

A. R. Touati, T. Homri, B. Ben Hassine
Faculté des Sciences, Laboratoire de Synthèse Organique et Photochimie, avenue de l'environnement, 5000 Monastir, Tunisie.

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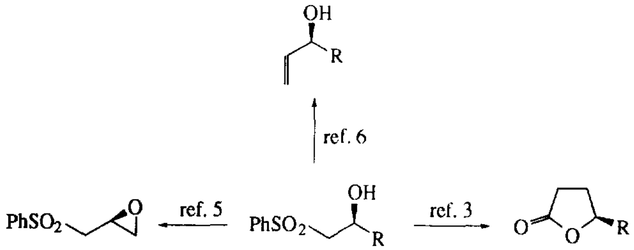
***Abstract:** A new ruthenium-promoted hydrogenation of β-keto sulfones using MeO-BIPHEP as ligand is reported with complete conversions and enantiomeric excesses over 95%.*

Hydroxy sulfones are useful chiral synthons in organic synthesis. Their preparation in enantiomerically pure form has attracted a considerable interest.[1,2] They have been successfully used in the synthesis of optically active lactones such as (*R*)-hexanolide or (*R*)-umbelactone[3] and γ-lactones.[4] They are also useful synthetic intermediates to obtain enantiomerically pure 2,5-disubstituted tetrahydrofuran units found in many natural products or chiral epoxides containing an electron-withdrawing sulfonyl group at the β-position.[5] Alkylation of the dianions of 1-(phenylsulfonyl) alkan-2-ols with electrophilic reagents has also been studied (Scheme 1).[6]



Scheme 1

Baker's yeast-mediated reduction of β-keto sulfones to the corresponding β-hydroxy sulfones has been reported.[7] Enantiomeric excesses were highly dependent on the substrate and especially on the size of the groups adjacent to the carbonyl. For example, 1-(phenylsulfonyl) propan-2-one was reduced to the (*S*)-alcohol in 98% yield and 95% e.e. If instead, the pentyl or phenyl analogues were submitted to microbial transformation, the corresponding hydroxy sulfones were obtained respectively in 10% and 15% e.e. (Scheme 1, R=n-C_5H_{11} or Ph).

E-mail:genet@ext.jussieu.fr

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This is one critical limitation of this reduction which resides in the substitution pattern of the carbonyl group of the β-keto sulfones.[7,8] The kinetic resolution of β-hydroxy sulfones has been achieved with porcine pancreatic lipase (PPL) with moderate selectivities.[9] Chemical methods for such reductions[10] have been also described which employed tartaric acid modified Raney nickel reagent leading to hydroxy sulfones in moderate 70% optical yield.[11]

The chiral Ru(II)-catalysts, readily prepared *in situ* from the commercially available CODRu(methylallyl)$_2$ and the chiral diphosphine by addition of methanolic HBr, are highly effective catalysts for the enantioselective hydrogenation of functionalized ketones to chiral alcohols. This method is advantageous for several reasons : wide scope, predictable absolute configurations, ready availability of the chiral Ru(II)-catalyst in either enantiomeric forms, simple process and high yields. Synthetic applications of this process include efficient syntheses of natural products or intermediates of biological interest.[12,13] We report here on a new application of the ruthenium-catalyzed asymmetric hydrogenation of β-keto sulfones using our simple *in situ* preparation of chiral Ru(II)-catalysts.[12]

All β-hydroxy sulfones were conveniently prepared through (*S*)-BINAP or (*S*)-MeO-BIPHEP /ruthenium catalyzed hydrogenations of the corresponding β-keto sulfones **1-6** easily accessible by condensation of the dianion of the methylphenylsulfone on various acid chlorides or esters.[14] We have found that the functionalized β-keto sulfones **1-4** were smoothly reduced at atmospheric pressure under optimized conditions (solvent, catalyst ratio, ligand) using 1 mol% of chiral ruthenium(II) catalyst in refluxing methanol. Our results are summarized in Table 1. Hydrogenation of the 1-(phenylsulfonyl) propan-2-one **1** to the (*R*)-1-(phenylsulfonyl)-propan-2-ol **7** proceeded with more satisfactory results using (*R*)-MeO-BIPHEP than (*R*)-BINAP (entries 1 and 2). Both enantiomers (*R*)-**7** and (*S*)-**8** were synthesized in enantiomerically pure forms respectively with (*R*) and (*S*)-MeO-BIPHEP (entries 2 and 3). The 1-(phenylsulfonyl) butan-2-one **2** was hydrogenated to the pure (*S*)-1-(phenylsulfonyl) butan-2-ol **9** again with (*S*)-MeO-BIPHEP (entry 4). In the hydrogenation reaction of 1-(phenylsulfonyl) heptan-2-one **3** promoted by ruthenium-BINAP complexes, both the activity and enantiomeric excess were moderate (entry 5, 82% e.e.). In contrast, excellent enantiofacial discrimination and complete conversion were observed with (*R*)-MeO-BIPHEP (entry 6, >95% e.e.) compared to baker's yeast-mediated reduction.[7] The asymmetric hydrogenation of β-keto sulfone **4** bearing a cyclohexyl ring proceeded smoothly in excellent e.e. affording (*R*)-1-(phenylsulfonyl)-2-cyclohexyl-ethan-2-ol **12**[15] with (*R*)-MeO-BIPHEP (entry 7, >95% e.e.). The ruthenium-mediated hydrogenation of β-keto sulfones **5** and **6** bearing respectively an alkyl long chain or an aromatic substituent required higher pressure : 1-(phenylsulfonyl) tridecan-2-one **5** and 1-(phenylsulfonyl)-2-acetophenone **6** were not completely hydrogenated at atmospheric pressure. When increasing the pressure to 10bar at 80°C, (*S*)-1-(phenylsulfonyl) tridecan-2-ol **13** was obtained with very high e.e. (entry 8, >95%,). Finally, the hydrogenation of 1-(phenylsulfonyl)-2-acetophenone **6** at 75bar and 80°C led to the corresponding β-hydroxy sulfone **14** in 89% e.e. (entry 9). In decreasing the temperature to 40°C, **14** was synthesized in an optically pure form (over 95%, entry 10).

In conclusion, the ruthenium-promoted hydrogenation reactions of β-keto sulfones have a wider scope and give in most cases higher e.e. values and yields than procedures using baker's yeast.[7] These reactions have been extended to preparative amounts (4 grams) of the starting β-keto sulfones. Furthermore, this process provides a practical and efficient route to both enriched enantiomeric forms of a wide range of β-hydroxy sulfones and this is the method of choice.

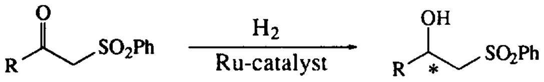
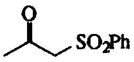
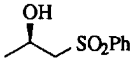
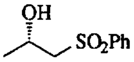
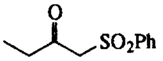
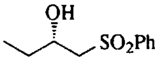
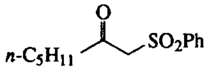
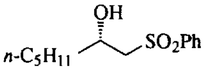
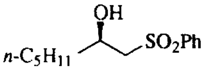
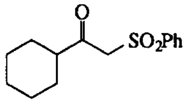
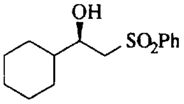
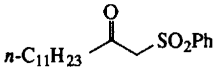
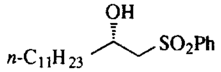
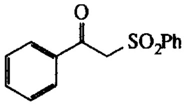
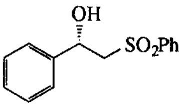


Table 1: Ruthenium-catalyzed hydrogenation of β-keto sulfones with (P*P)RuBr$_2$[a]

Entry	Substrate	Ligand (P*P)	Product[b,c]	Conv.[d]	e.e.[e]
1	 **1**	(*R*)-BINAP	 **7**	90	91
2		(*R*)-MeO-BIPHEP		100	>95[f]
3	**1**	(*S*)-MeO-BIPHEP	 **8**	100	>95[f]
4	 **2**	(*S*)-MeO-BIPHEP	 **9**	100	>95[f]
5	 **3**	(*S*)-BINAP	 **10**	67	82
6	**3**	(*R*)-MeO-BIPHEP	 **11**	100	>95[f]
7	 **4**	(*R*)-MeO-BIPHEP	 **12**	100	>95[f]
8	 **5**	(*S*)-MeO-BIPHEP[g]	 **13**	100	>95[f]
	 **6**		 **14**		
9	**6**	(*S*)-MeO-BIPHEP[h]	**14**	100	89
10	**6**	(*S*)-MeO-BIPHEP[i]	**14**	100	>95[f]

(a) Chiral Ru (II) catalyst (1% mol). (b) The absolute configurations of the β-hydroxy sulfones were assigned by comparison of their specific rotations with those described in the literature[7,17] except for compound 9.[4a,16] (c) Reaction times: 18 to 65 h. (d) Conversions were determined by ^1H NMR. (e) e.e. were determined by ^1H NMR (250MHz) with Eu(Tfc)$_3$. (f) Only one enantiomer was detectable by ^1H NMR (250MHz or 400MHz) with Eu(Tfc)$_3$. (g) Hydrogenation conducted at 10bar and 80°C for 18h using 2% mol catalyst. (h) Hydrogenation conducted at 75bar and 80°C for 48h. (i) Hydrogenation conducted at 75bar and 40°C for 48h.

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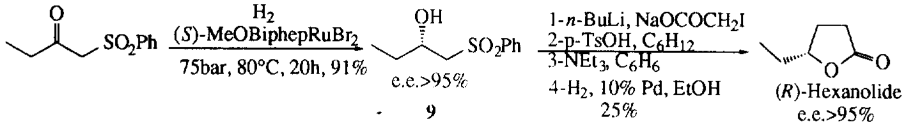
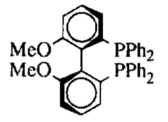
References

1. *The Chemistry of Sulfur-Containing Functional Groups*; Patai, S., Rappoport, Z. Eds.; Wiley Interscience: New York, **1993**. Oae, S. *Organic Sulfur Chemistry;* CRC Press: Boca Raton, **1991**. *Chemistry of Organosulfur Compounds*; Belen'Kii, L. I., Ed.; Ellis Horwood: New York, **1990**.
2. Simpkins, N. S. *Sulphones in Organic Synthesis* Pergamon Press: New York, **1993**.
3. Sato, T.; Okumura, Y.; Itai, J.; Fujisawa, T. *Chem. Lett.* **1988**, 1537-1540.
4. a) Kozikowski, A. P.; Mugrage, B. B.; Li, C. S.; Felder, L. *Tetrahedron Lett.* **1986**, *27*, 4817-4820. b) For a recent synthesis of γ-lactones using asymmetric dihydroxylation see : Harcken, C.; Brückner, R.; Rank, E. *Chem. Eur. J.* **1998**, *4*, 2342-2352.
5. Tanikaga, R.; Hosoka, K.; Kaji, A. *J. Chem. Soc. Perkin Trans. I* **1987**, 1799-1803.
6. a) Tanikaga, R.; Hosoya, K.; Kaji, A. *J. Chem. Soc. Perkin Trans. I* **1988**, 2397-2402. b) Tanikaga, R.; Hosoya, K.; Kaji, A. *Chem. Lett.* **1987**, 829-832.
7. a) Reviews on baker's yeast reductions including examples of ketones bearing sulfur groups: Servi, S. *Synthesis* **1990**, 1-25. Csuk, R.; Glänzer, B. I. *Chem. Rev.* **1991**, *91*, 49-97 and references cited therein. See also b) Crumbie, R. L.; Deol, B. S.; Nemorin, J. E.; Ridley, D. D. *Aust. J. Chem.* **1978**, *31*, 1965-1980.
8. Nakamura, K.; Ushio, K.; Oka, S.; Ohno, A.; Yasui S. *Tetrahedron Lett.* **1984**, *25*, 3979-3982.
9. Chinchilla R.; Najera, C.; Pardo, J.; Yus, M. *Tetrahedron: Asymmetry* **1990**, *1*, 575-578.
10. One example of reduction of γ-keto sulfone has been reported with chiral oxazaborolidine in e.e. up to 98%. See Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611-614.
11. Hiraki, Y.; Ito, K.; Harada, T.; Tai, A. *Chem. Lett.* **1981**, 131-132.
12. a) Ratovelomanana-Vidal, V.; Genêt, J. P. *J. Organomet. Chem.* **1998**, *567*, 163-171. b) Genêt, J.-P.; Ratovelomanana-Vidal, V.; Caño de Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* **1995**, *36*, 4801-4804. c) Genêt, J.-P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Caño de Andrade, M. C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 665-674. d) Genêt, J.-P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Bischoff, L.; Caño de Andrade, M. C.; Darses, S.; Galopin, C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 675-690.
13. For reviews about chiral Ru-catalysts, see a) Genêt, J.-P. in *Reductions in Organic Synthesis in A.C.S. Symposium series 641*, **1996**, pp 31-51. A. F., Abdel Magid Ed. b) Genêt, J.-P. *Acros Organics Acta*, **1995**, *1*, 4-9. c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; J. Wiley: N.Y., **1994**, pp 1-93. d) Noyori, R. *Acc. Chem. Res.* **1997**, *30*, 97-102.
14. a) Berdardi, R; Bravo, P.; Cardillo, R.; Ghiringhelli, D.; Resnati, G. *J. Chem. Soc. Perkin Trans. I* **1988**, 2831-2834. b) Thomsen, M. W.; Handwerker, B. M.; Katz, S. A.; Belser, R. B. *J. Org. Chem.* **1988**, *53*, 906-907.
15. Characteristic data for compound **12** : ^{1}H NMR (250MHz, $CDCl_3$) : δ = 0.95-1.90 (11H, m), 3.20-3.30 (2H, m), 3.91-3.98 (1H, m), 7.55-7.73 (3H, m), 7.91-7.96 (2H, m). ^{13}C NMR (50MHz, $CDCl_3$) : δ = 25.8, 25.9, 26.1, 27.4, 28.4, 43.1, 60.2, 69.7, 127.8, 129.4, 133.9, 139.2. M.S. (E. I.) m/e = 269 (5, $M\text{-}H^+$), 185 (100), 141 (55). $[\alpha]_D$ = -20 (c=1, $CHCl_3$).
16. The absolute configuration of **9** was established by correlation with (*R*)-hexanolide, a component of the pheromone secreted by the female dermisted beetle *Trogoderma glabrum* using the following sequence. The e.e. of (*R*)-hexanolide was measured by chiral GC (Megadex 5 column) with an optical rotation in accord with literature data.[3]



17. Iriuchijima, S.; Kojima, N. *Agric. Biol. Chem.*, **1978**, *42*, 451-455.
18. We are grateful to Dr. R. Schmid (Hoffmann La Roche) for samples of (*R*)-MeO-BIPHEP = (*R*)-(+)-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl and (*S*)-MeO-BIPHEP.



(*R*)-MeO-BIPHEP